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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,832	08/17/2006	Toshiyuki Takahashi	BY0037P	2766

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,832	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 23-37 drawn to compound of formula I wherein k=0 and j=1, composition and method of use, in the reply filed on 11/7/2008 is acknowledged. Claims 23-37 will be examined to the extent they embrace the elected subject matter.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 8/17/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-37 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Regarding claim 23, the phrase "preferably" renders the claim 23 and its dependent claims 24-37 indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for obesity does not reasonably provide enablement for treating any or all metabolic diseases, circulatory diseases and nervous system diseases as embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." See MPEP 2164.01(a). The factors to be considered in making an enablement rejection have been summarized below.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention:

The instant method of use claim 34 is drawn to a metabolic system disease, a circulatory system disease or a nervous system disease in a mammalian patient in general based on the mode of action of instant compounds as histamine H3 receptor antagonists while claim 35 is drawn specific circulatory diseases such as stenocardia, acute/congestive cardiac insufficiency, cardiac infarction, coronary arteriosclerosis,

hypertension, nephropathy and electrolyte metabolism disorder and claim 36-36 are drawn to specific nervous system diseases such as a sleep disorder, bulimia, emotional disorder, epilepsy, delirium, dementia, attention deficit/hyperactivity disorder, memory disorder, Alzheimer's disease, Parkinson's disease, recognition disorder, motion disorder, paresthesia, dysosmia, morphine resistance, narcotic dependency, alcoholic dependency and tremor idiopathic hypersomnnia, repetitive hypersomnnia, true hypersomnnia, narcolepsy, sleep periodic acromotion disorder, sleep apnea syndrome, circadian rhythm disorder, chronic fatigue syndrome, REM sleep disorder, senile insomnia, night worker sleep insanitation, idiopathic insomnia, repetitive insomnia, true insomnia, melancholia, anxiety and schizophrenia.

Instant claims 34-37, as recited, are reach through claim. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of Histamine H3 receptor activity in general by the instant compounds, claims 34-37 reach through treating any or all diseases mediated by Histamine H3 receptor in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as antagonists of Histamine H3 receptor, based on limited in vitro assay it is claimed that treating any or all metabolic diseases, circulatory diseases and nervous

system diseases including those specific diseases stated above, for which there is no enabling disclosure.

In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 95-96. The instant compounds are disclosed to have histamine H3 receptor inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as histamine H3 receptor inhibitor that would be useful for all sorts of diseases and disorders stated above. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as Alzheimer's disease Parkinson's disease, multiple sclerosis etc. are very difficult to treat and despite the fact that there are many drugs, which can be used for "inflammatory condition".

The scope of the claims involves all of the millions of compounds of claim 23 as well as the thousands and thousands of diseases embraced in claims 34-37.

There are hundreds and hundreds of such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad. The claims cover methods for treatment of all of the diseases mentioned above, including other diseases that may be discovered in the future that may be comprehended under the recited diseases.

No compound has ever been found to treat any or all diseases and disorders and cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. The specification fails to identify the results of treatment with the methods of this invention and how such results would be recognized, particularly with regard to conditions and diseases that are currently considered incurable, untreatable or fatal.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Hancock et al., cited below.

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue

experimentation is involved in determining those that are operative.". Clearly that is the case here.

2) The state of the prior art: Recent publication, Hancock et al, expressed that the Histamine receptor inhibition effects are unpredictable and are still exploratory. Hancock states in concluding paragraph clearly states need for further experimentation. Given the breadth of instant claims such experimentation would be unduly extensive.

Hence, in the absence of showing of correlation between all the diseases claimed as capable of treatment with inhibition of altered protein kinase activity, one of skill in the art is unable to fully predict possible results from the administration of the compounds of formula (I) due to the unpredictability of the role of the instantly claimed compounds. For example, since it is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumor with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy.

Applicant's disclosure does not enable one of ordinary skill in the art to use the claimed invention within the entire scope of the diseases listed above. There is no compound, let alone an entire class of compounds that can treat the various and divergent diseases listed above, as claimed.

Those of skill in the art recognize that in vitro assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly

increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present:

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. The only direction or guidance present in the specification is the listing of diseases applicant considers treatable. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art to extrapolate to the other compounds of the claims.

The disclosure does not provide how this in vitro data correlates to the treatment of the assorted diseases claimed. The instant specification is short of any examples or data in regards to the supposed treating of the aforementioned diseases. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and diseases stated above and the state of the art is that the effects of histamine receptor inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all diseases or disorders stated above including those yet to be related to histamine receptor activity.

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of the instant claims for the treatment of the various claimed diseases as a result necessitating one of skill to perform an exhaustive search for which disorders can

be treated by what compounds of the instant claims in order to practice the claimed invention.

8) The quantity of experimentation: The quantity of experimentation needed is undue experimentation. It would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above. One of skill in the art would need to determine what diseases out of the multitude claimed would be benefited (i.e. treated) by the administration of the compounds of formula (I) and would furthermore have to determine which of the claimed compounds would provide treatment of which disease.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling

disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds encompassed in the instant claims, with no assurance of success.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624